REMARKS

The Office Action dated July 16, 2004, has been received and reviewed. Claims 1-2, 5-9, 12-24, 26-29 and 32 are pending in the present application. Claims 1-2, 5-9, 12-24 and 26 stand rejected. Applicants respectfully request reconsideration of the application in view of the amendments made and the arguments below.

I. Specification Objections

Applicants have amended the specification as suggested by the Examiner to correct for informalities and to correct for other informal errors. Accordingly, Applicants submit that the specification is in proper order.

II. Claim Amendments

Claim 24 has been amended as suggested by the Examiner. Applicants submit that no new matter has been raised by these amendments.

III. Rejections under 35 U.S.C. § 112, second paragraph

Claims 24 and 26 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants have amended claim 24 to correct for a spelling error and to provide proper antecedent basis. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to claim 24 and dependent claim 26.

IV. Rejections under 35 U.S.C. § 103(a)

A. Barak et al and Siegel et al. in view of Liaw et al.

Claims 1-2, 6-9, 13-17 and 20-22 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barak et al. (Molec. Pharma. 2, 177, 1997) and Siegel et al. (U.S. Patent No. 6,660,844) in view of Liaw et al. (U.S. Patent No. 6,555,339). Applicants traverse this rejection for the amended claims for the reasons set forth below.

To establish a prima facie case of obviousness, the prior art reference or references when combined must teach or suggest *all* the recitations of the claim, and there must be some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). To support combining references, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Court of Appeals for the Federal Circuit has also stated that, to support combining or modifying references, there must be particular evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Furthermore, as affirmed by the Court of Appeals for the Federal Circuit in *In re Sang-su Lee*, a factual question of motivation is material to patentability, **and cannot be resolved on subjective belief and unknown authority**. *See In re Sang-su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). Respectfully, as will be discussed below, the Official Action fails to meet the requirements for a prima facie showing of obviousness under § 103.

Barak et al. merely describes fusions between beta2-andrenergic receptor and GFP. The receptor protein used in Barak et al. are wild type proteins. The claims of the present application recite a constitutively active mutant which is not taught or anticipated in Barak et al. Similarly, Siegel et al. fails to anticipate a constitutively active mutant. Siegel et al. also fails to teach a fusion protein comprising a membrane receptor segment and a reporter segment wherein the membrane receptor segment is a constitutively active mutant receptor.

Applicants submit that Liaw et al. describes a method for generating constituently active mutants (CAMs) of G-protein coupled receptors (CAM GPCRs) using an algorithmic approach. Liaw et al. observes that CAM GPCRs are well-suited for assays of GPCR function because the ligand for the receptor need not be present for the receptor to function. This makes CAM GPCRs suitable for study even of orphan receptors for which the physiological ligand is unknown. Liaw et al. suggests that CAM GPCRs can be used for screening candidate compounds for their effect on GPCRs. These techniques are described

e.g. at column 13, line 14 to column 14, line 37, and also at column 36, line 19 to column 39, line 61. However these techniques rely on the biological effects of the GPCR, such as their ability to activate G proteins. Thus, the techniques described in Liaw et al. rely on the downstream effects of receptor function and do not rely on "detecting a signal from the reporter segment" as recited in claim 1 of the present application.

Liaw describes (column 13, line 46 to column 14, line 16) an assay which uses a reporter protein such as luciferase. However, the reporter protein is not fused to the receptor protein. Instead, it is encoded by a reporter gene placed under the control of a cyclic AMP-responsive regulatory element. Activation of adenylate cyclase by the CAM GPCR and associated G protein leads to production of cAMP, which binds to a transcription factor (CREB), which in turn stimulates transcription of the reporter gene. Thus, it can be determined that these assays are fundamentally different to the currently claimed methods in which the reporter protein is fused to the receptor itself.

Furthermore, Applicants note that the present invention is partially based on the fact that CAM GPCRs are more unstable than wild type receptors. Although the receptors are constantly being produced, they are also constantly recycled from the membrane into the cell and destroyed at a much higher rate than the wild type receptor (page 27, lines 1 to 14 and page 4, lines 5 to 19). These concepts are not mentioned in Liaw, and there is certainly nothing in Liaw to show the skilled person how they could usefully be applied. Rather, Liaw is motivated to use CAM GPCRs because they obviate the need for a ligand to study activity of the receptor. The teaching of Liaw therefore provides no motivation for the skilled person to perform screening assays based on a change in receptor stabilization or cellular localization as detected by a reporter fused to the receptor itself.

B. Siegel et al. and Barak et al. in view of Liaw et al. and in view of Leurs et al.

Claims 5, 12 and 26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barak et al. and Siegel et al. in view of Liaw et al. and in view of Leurs et al. (TIBS, 23 418 1998). Applicants traverse this rejection for the reasons set forth below.

As noted above, Barak et al. does not teach or suggest the use of constitutively active mutants. Furthermore, Leurs et al. fails to teach or suggest the elements of the present invention. Applicants submit that Leurs et al. describes various properties of constituently

active mutants (CAMs) of G-protein coupled receptors but make no suggestion as to how these properties could be usefully applied. Furthermore, Leurs et al. fails to contain any motivation to generate a fusion protein between a CAM and a reporter protein, much less use such a fusion protein in an assay as claimed in the present application. Applicants submit that the present invention is the first to realize the properties of CAMs that can be exploited to provide a test for compounds which modulate membrane receptor protein activity. Applicants note that CAM has a short half-life compared to a wild-type receptor. Thus, although the CAM receptors are constantly being produced, they are also constantly being internalized from the membrane into the cell and are being destroyed at a much higher rate than the wild-type receptor. Leurs et al. fails to suggest or teach that these properties can be exploited to produce the assay as presently claimed. Leurs et al. fails to teach or suggest that CAMs can be successfully used in an assay to determine the effect of a test compound on a membrane receptor. Because of the inherent instability of CAM receptors, the effect of any given test compound on the activity of a Cam receptor/reporter fusion protein will be much greater than it would be as compared to the activity of a wild type receptor/reporter fusion protein. Thus, Leurs et al. fails to contain the motivation to combine itself with Barak to teach the elements of the present claims.

Applicants submit that as noted above, neither Barak et al. nor Leurs et al. either alone or in combination teach or suggest the elements of the claims of the present application. Furthermore, Siegel et al. as noted above, fails to disclose all of the elements of the claims of the present invention. Siegel et al. provides a kit for determining the presence of an activity in a sample, including either a chimeric protein of the invention, or a nucleic acid sequence encoding a chimeric protein of the invention. The example provided by Siegel et al. illustrates a responsive polypeptide that is a voltage-gated ion channel and an optically active polypeptide, a deletion mutant of GFP. In contrast, the claims of the present invention recite an assay for detecting an effect a compound has on a membrane receptor byadding the compound to a cell expressing a membrane receptor/reporter fusion protein, the fusion protein comprising a membrane receptor segment and a reporter segment; and detecting any change of said receptor/reporter fusion protein by detecting a signal from the reporter segment; wherein the membrane receptor segment is a constitutively active mutant receptor. Sigel et al. fails to teach or suggest any such assay. Furthermore, Siegal et al. in view of

Barak et al. and Leurs et al. fail to teach or suggest such an assay. Accordingly, Applicants respectfully request reconsideration of the rejection of Claims 5, 12 and 24 under 35 U.S.C. § 103(a).

Furthermore, Liaw et al. fails to teach or suggest the elements of the present application as it merely discloses the activation of adenylate cyclase by the CAM GPCR and associated G protein leads to production of cAMP, which binds to a transcription factor (CREB), which in turn stimulates transcription of the reporter gene. Thus, the assays of Liaw et al. are fundamentally different to the currently claimed methods in which the reporter protein is fused to the receptor itself. Thus, there is no motivation in any of the prior art documents to carry out a screening method as currently claimed, and that the claimed methods are not obvious over the art cited. Applicants note that the Examiner has already acknowledged that there is no motivation to combine Leurs with Barak and Siegal. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 5, 12 and 26.

C. In view of Bryan et al.

Claims 18-19 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Barak et al. and Siegel et al. in view of Liaw et al. and in view of Leurs et al. in view of Bryan et al., U.S. Patent No. 6,232,107. Applicants traverse this rejection for the amended claims for the following reasons. As noted above, Barak et al., Siegel et al., Liaw et al., and Leurs et al. fail to teach or suggest the elements of the present invention as presently claimed either alone or in combination with one another. Similarly, Bryan et al., either alone or in combination with Barak et al., fails to teach the elements of the claims of the present invention. Bryan et al. provides isolated nucleic acids that encode fluorescent proteins and nucleic acids that encode luciferases. Bryan et al. does not teach or suggest the assay as claimed which detects any change of said receptor/reporter fusion protein by detecting a signal from the reporter segment; wherein the membrane receptor segment is a constitutively active mutant receptor. Furthermore, the combination of Barak et al., Siegel et al., Liaw et al., and Leurs et al. with Bryan et al. would still not teach or suggest the elements of the present invention as again they both fail to teach or suggest an assay which detects any change of said receptor/reporter fusion protein by detecting a signal from the reporter segment, wherein

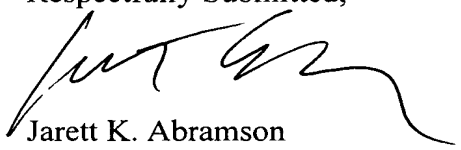
the membrane receptor segment is a constitutively active mutant receptor as presently claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejections to claims 18-19 and 23.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,



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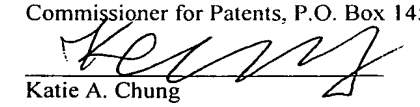

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